IN THE SPECIFICATION

At page 3, please replace lines 1-7 with the following text:

In one embodiment, the invention features an isolated nucleic acid molecule that includes the nucleotide sequence set forth in SEQ ID NO:1 or SEQ ID NO:3. In another embodiment, the invention features an isolated nucleic acid molecule that encodes a polypeptide including the amino acid sequence set forth in SEQ ID NO:2. ~~In another embodiment, the invention features an isolated nucleic acid molecule that includes the nucleotide sequence contained in the plasmid deposited with ATCC® as Accession Number _____.~~

At page 7, please replace lines 7-27 with the following text:

~~*Figures 1A-1B* depict the nucleotide sequence of human COE-2 cDNA and the corresponding amino acid sequence. The nucleotide sequence corresponds to nucleic acids 1 to 1983 of SEQ ID NO:1. The amino acid sequence corresponds to amino acids 1 to 584 of SEQ ID NO:2. The coding region without the 5' or 3' untranslated regions of the human COE-2 gene is shown in SEQ ID NO:3.~~

Figure 1~~*Figure 2*~~ depicts a structural, hydrophobicity, and antigenicity analysis of the human COE-2 protein.

Figures 2A-2C~~*Figures 3A-3B*~~ depict the results of a search in the HMM database, using the amino acid sequence of human COE-2. This search resulted in the identification of a carboxylesterase domain (COesterase) in the human COE-2 protein.

Figures 3A-3D~~*Figures 4A-4D*~~ depict a global alignment of the cDNA nucleotide sequence of human COE-2 with that of human PRO873 (Accession No. Z34105 in the Patent Nucleotide database) (SEQ ID NO:6).

Figures 4A-4C~~*Figures 5A-5B*~~ depict a global alignment of the amino acid sequence of human COE-2 with that of human PRO873 (SEQ ID NO:7).

Figures 5A-5B depict~~*Figure 6* depicts~~ the expression of COE-2 in various tissues as determined with TAQman assays. Relatively high expression in brain and spinal cord is evident.

Figures 6A-6B depict~~*Figure 7* depicts~~ the expression of COE-2 in tissues from various organisms as determined with TAQman assays. High expression is evident in brain and spinal cord.

Figures 7A-1 through 7B~~*Figures 8A-8B*~~ depict the expression of COE-2 in various normal and tumor tissues as determined with TAQman assays. High expression is evident in brain.

At pages 7-8, please replace the paragraph at page 7, line 29 through page 8, line 7 with the following text:

Detailed Description of the Invention

The present invention is based, at least in part, on the discovery of novel carboxylesterase family members, referred to herein as "Carboxylesterase-2" or "COE-2" nucleic acid and protein molecules. These novel molecules are capable of participating in the metabolism of various lipid and fatty acid compounds which are involved in pain and/or inflammation signaling, *e.g.*, arachidonic acid and related eicosanoids, diacyl glycerol, lysophosphatidic acid, lysophosphatidylcholine, and endocannabinoids, *e.g.*, anandamide and 2-AG. The present invention is also based, at least in part, on the discovery that these molecules are highly expressed in tissues which contain afferent neurons, particularly brain and spinal cord tissue (Figures 5-7~~Figures 6-8~~). In mammals, the initial detection of noxious chemical, mechanical, or thermal stimuli, a process referred to as "nociception", occurs predominantly at the peripheral terminals of specialized, small diameter primary afferent neurons, called polymodal nociceptors. These afferent neurons transmit the information to the central nervous system, evoking a perception of pain or discomfort and initiating appropriate protective reflexes. Thus, the COE-2 molecules of the present invention may participate in pain-signaling mechanisms and, as such, may modulate pain elicitation and provide novel diagnostic targets and therapeutic agents for inflammatory or pain disorders.

At page 9, please replace the paragraph at lines 24-36 with the following text:

In one embodiment, the COE-2 proteins of the present invention contain at least one transmembrane domain. As used herein, the term "transmembrane domain" includes an amino acid sequence having at least about 10, preferably about 13, preferably about 16, more preferably about 19, 21, 23, 25, 30, 35 or 40 amino acid residues, of which at least about 50-60%, 60-70%, preferably about 70-80% more preferably about 80-90%, or about 90-95% of the amino acid residues contain non-polar side chains, for example, alanine, valine, leucine, isoleucine, proline, phenylalanine, tryptophan, and methionine. A transmembrane domain is lipophilic in nature. Transmembrane domains are described in, for example, Zagotta *et al.*, (1996) *Annual Rev. Neurosci.* 19:235-63, the contents of which are incorporated herein by reference. In a preferred embodiment, a COE-2 protein of the present invention has more than one transmembrane domain, preferably 2 transmembrane domains. Transmembrane domains were identified at about amino acids 26-45 and 245-263 of SEQ ID NO:2 (see Figure 1~~Figure 2~~).

At pages 9-10, please replace the paragraph at page 9, line 37 through page 10, line 15 with the following text:

Members of the COE-2 family of proteins may also be identified by the presence of at least one "carboxylesterase domain" in the protein or corresponding nucleic acid molecule. As used herein, the term "carboxylesterase domain" includes a protein domain having at least about 440-600 amino acid residues and a bit score of at least 440 when compared against a carboxylesterase Hidden Markov Model (HMM), *e.g.*, PFAM Accession Number PF00135. Preferably, a carboxylesterase domain includes a protein having an amino acid sequence of about 505-585, 525-565, 535-555, or more preferably about 545 amino acid residues, and a bit score of at least 250, 350, 450, 500, or more preferably, 558.6. To identify the presence of a carboxylesterase domain in a COE-2 protein, and make the determination that a protein of interest has a particular profile, the amino acid sequence of the protein is searched against a database of known protein domains (*e.g.*, the HMM database). The carboxylesterase domain (HMM) has been assigned the PFAM Accession number PF00135 (see the Pfam website) and the InterPro Accession number IPR002018 (see the InterPro website). A search was performed against the HMM database resulting in the identification of a carboxylesterase domain in the amino acid sequence of human COE-2 at about residues 25-569 of SEQ ID NO:2. The results of the search are set forth in Figure 2~~Figure 3~~.

At page 11, please replace lines 20-38 with the following text:

In a preferred embodiment, a COE-2 protein includes at least one or more of the following four features: a carboxylesterase domain, a transmembrane domain, a carboxylesterase B1 signature motif, a carboxylesterase B2 signature motif, and has an amino acid sequence at least about 50%, 55%, 60%, 63%, 65%, 70%, 75%, 80%, 85%, 85%, 90%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more homologous or identical to the amino acid sequence of SEQ ID NO:2~~, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~. In yet another preferred embodiment, a COE-2 protein includes at least one or more of the following four features: a carboxylesterase domain, a transmembrane domain, a carboxylesterase B1 signature motif, a carboxylesterase B2 signature motif, and is encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a complement of a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1 or 3. In another preferred embodiment, a COE-2 protein includes at least one or more of the following four features: a carboxylesterase domain, a transmembrane domain, a carboxylesterase B1 signature motif, a carboxylesterase B2 signature motif, and is at least 273 amino acids in length. In another preferred embodiment, a COE-2 protein includes at least one or more of the following four features: a carboxylesterase domain, a transmembrane domain, a carboxylesterase B1 signature motif, a carboxylesterase B2 signature motif, and has a COE-2 activity.

At page 12, please replace the paragraph at lines 27-35 with the following text:

The nucleotide sequence of the isolated human COE-2 cDNA and the predicted amino acid sequence encoded by the COE-2 cDNA are shown in ~~Figure 1 and in~~ SEQ ID NO:1 and 2, respectively. ~~A plasmid containing the human COE-2 cDNA was deposited with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA 20110-2209, on _____ and assigned Accession Number _____. This deposit will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. This deposit were made merely as a convenience for those of skill in the art and is not an admission that a deposit is required under 35 U.S.C. §112.~~

At pages 13-14, please replace page 13, line 29 through page 14, line 8 with the following text:

A nucleic acid molecule of the present invention, *e.g.*, a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1 or 3, or a complement thereof, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, or a portion thereof, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or a portion of the nucleic acid sequence of SEQ ID NO:1 or 3, or a complement thereof, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, as hybridization probes, COE-2 nucleic acid molecules can be isolated using standard hybridization and cloning techniques (*e.g.*, as described in Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual. 2nd, ed., Cold Spring Harbor Laboratory,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

Moreover, a nucleic acid molecule encompassing all or a portion of SEQ ID NO:1 or 3, or a complement thereof, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~ can be isolated by the polymerase chain reaction (PCR) using synthetic oligonucleotide primers designed based upon the sequence of SEQ ID NO:1 or 3~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~ .

At pages 14-15, please replace page 14, line 28 through page 15, line 31 with the following text:

In still another embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which is a complement of the nucleotide sequence shown in SEQ ID NO:1 or 3, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, or a portion of any of these nucleotide sequences. A nucleic acid molecule which is complementary to the nucleotide sequence shown in SEQ ID NO:1 or 3, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, is one which is sufficiently complementary to the nucleotide sequence shown in SEQ ID NO:1 or 3, ~~or the nucleotide~~

~~sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, such that it can hybridize to the nucleotide sequence shown in SEQ ID NO:1 or 3, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, thereby forming a stable duplex.

In still another embodiment, an isolated nucleic acid molecule of the present invention comprises a nucleotide sequence which is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the nucleotide sequence shown in SEQ ID NO:1 or 3 (*e.g.*, to the entire length of the nucleotide sequence), ~~or to the nucleotide sequence (e.g., the entire length of the nucleotide sequence) of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, or a portion or complement of any of these nucleotide sequences. In one embodiment, a nucleic acid molecule of the present invention comprises a nucleotide sequence which is at least (or no greater than) 50, 100, 250, 300, 400, 600, 800, 828, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 1950, or more nucleotides in length and hybridizes under stringent hybridization conditions to a complement of a nucleic acid molecule of SEQ ID NO:1 or 3~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~.

Moreover, the nucleic acid molecule of the invention can comprise only a portion of the nucleic acid sequence of SEQ ID NO:1 or 3, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, for example, a fragment which can be used as a probe or primer or a fragment encoding a portion of a COE-2 protein, *e.g.*, a biologically active portion of a COE-2 protein. The nucleotide sequence determined from the cloning of the COE-2 gene allows for the generation of probes and primers designed for use in identifying and/or cloning other COE-2 family members, as well as COE-2 homologues from other species. The probe/primer (*e.g.*, oligonucleotide) typically comprises substantially purified oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12 or 15, preferably about 20 or 25, more preferably about 30, 35, 40, 45, 50, 55, 60, 65, or 75 consecutive nucleotides of a sequence of SEQ ID NO:1 or 3, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, or of a naturally occurring allelic variant or mutant of SEQ ID NO:1 or 3, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, or to complements of any of the aforementioned.

At page 16, please replace lines 14-36 with the following text:

A nucleic acid fragment encoding a "biologically active portion of a COE-2 protein" can be prepared by isolating a portion of the nucleotide sequence of SEQ ID NO:1 or 3, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, which encodes a polypeptide having a COE-2 biological activity (the biological activities of the COE-2 proteins are described herein), expressing the encoded portion of the COE-2 protein (*e.g.*, by recombinant

expression *in vitro*) and assessing the activity of the encoded portion of the COE-2 protein. In an exemplary embodiment, the nucleic acid molecule is at least 50-100, 100-250, 250-500, 500-750, 750-1000, 1000-1250, 1250-1500, 1500-1750, 1750-1950 or more nucleotides in length and encodes a protein having a COE-2 activity (as described herein).

The invention further encompasses nucleic acid molecules that differ from the nucleotide sequence shown in SEQ ID NO:1 or 3, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, due to degeneracy of the genetic code and thus encode the same COE-2 proteins as those encoded by the nucleotide sequence shown in SEQ ID NO:1 or 3~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~. In another embodiment, an isolated nucleic acid molecule of the invention has a nucleotide sequence encoding a protein having an amino acid sequence which differs by at least 1, but no greater than 5, 10, 20, 50 or 100 amino acid residues from the amino acid sequence shown in SEQ ID NO:2~~, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with the ATCC as Accession Number _____~~. In yet another embodiment, the nucleic acid molecule encodes the amino acid sequence of human COE-2. If an alignment is needed for this comparison, the sequences should be aligned for maximum homology.

At page 17, please replace lines 13-18 with the following text:

Accordingly, in one embodiment, the invention features isolated nucleic acid molecules which encode a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, ~~or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, wherein the nucleic acid molecule hybridizes to a complement of a nucleic acid molecule comprising SEQ ID NO:1 or 3, for example, under stringent hybridization conditions.

At page 18, please replace lines 3-13 with the following text:

Moreover, nucleic acid molecules encoding other COE-2 family members and, thus, which have a nucleotide sequence which differs from the COE-2 sequences of SEQ ID NO:1 or 3~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~ are intended to be within the scope of the invention. For example, another COE-2 cDNA can be identified based on the nucleotide sequence of human COE-2. Moreover, nucleic acid molecules encoding COE-2 proteins from different species, and which, thus, have a nucleotide sequence which differs from the COE-2 sequences of SEQ ID NO:1 or 3~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~ are intended to be within the scope of the invention. For example, a mouse or monkey COE-2 cDNA can be identified based on the nucleotide sequence of a human COE-2.

At page 18, please replace lines 21-29 with the following text:

Orthologues, homologues and allelic variants can be identified using methods known in the art (*e.g.*, by hybridization to an isolated nucleic acid molecule of the present invention, for example, under stringent hybridization conditions). In one embodiment, an isolated nucleic acid molecule of the invention is at least 15, 20, 25, 30 or more nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1 or 3~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~. In other embodiments, the nucleic acid is at least 50, 100, 250, 300, 400, 600, 800, 828, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 1950 or more nucleotides in length.

At pages 19-20, please replace page 19, line 37 through page 20, line 15 with the following text:

In addition to naturally-occurring allelic variants of the COE-2 sequences that may exist in the population, the skilled artisan will further appreciate that changes can be introduced by mutation into the nucleotide sequences of SEQ ID NO:1 or 3, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, thereby leading to changes in the amino acid sequence of the encoded COE-2 proteins, without altering the functional ability of the COE-2 proteins. For example, nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues can be made in the sequence of SEQ ID NO:1 or 3~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence of COE-2 (*e.g.*, the sequence of SEQ ID NO:2) without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are conserved among the COE-2 proteins of the present invention, *e.g.*, those present in carboxylesterase domain, are predicted to be particularly unamenable to alteration. Furthermore, additional amino acid residues that are conserved between the COE-2 proteins of the present invention and other members of the carboxylesterase family are not likely to be amenable to alteration.

At pages 20-21, please replace page 20, line 24 through page 21, line 11 with the following text:

An isolated nucleic acid molecule encoding a COE-2 protein homologous to the protein of SEQ ID NO:2 can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of SEQ ID NO:1 or 3, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, such that one or more amino acid substitutions, additions or deletions are introduced into the encoded protein. Mutations can be introduced

into SEQ ID NO:1 or 3~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~ by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in a COE-2 protein is preferably replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of a COE-2 coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for COE-2 biological activity to identify mutants that retain activity. Following mutagenesis of SEQ ID NO:1 or 3, ~~or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~, the encoded protein can be expressed recombinantly and the activity of the protein can be determined.

At page 23, please replace lines 19-34 with the following text:

In still another embodiment, an antisense nucleic acid of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes (described in Haselhoff and Gerlach (1988) *Nature* 334:585-591)) can be used to catalytically cleave COE-2 mRNA transcripts to thereby inhibit translation of COE-2 mRNA. A ribozyme having specificity for a COE-2-encoding nucleic acid can be designed based upon the nucleotide sequence of a COE-2 cDNA disclosed herein (*i.e.*., SEQ ID NO:1 or 3~~, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~). For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in a COE-2-encoding mRNA. See, *e.g.*, Cech *et al.* U.S. Patent No. 4,987,071; and Cech *et al.* U.S. Patent No. 5,116,742. Alternatively, COE-2 mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. See, *e.g.*, Bartel, D. and Szostak, J.W. (1993) *Science* 261:1411-1418.

At page 26, please replace lines 29-37 with the following text:

Another aspect of the invention features fragments of the protein having the amino acid sequence of SEQ ID NO:2, for example, for use as immunogens. In one embodiment, a fragment comprises at least 5 amino acids (*e.g.*, contiguous or consecutive amino acids) of the amino acid sequence of SEQ ID NO:2~~, or an amino acid sequence encoded by the DNA insert of the plasmid deposited with the ATCC as Accession Number _____~~. In another embodiment, a fragment comprises at least 10, 15, 20, 25, 30, 35, 40, 45, 50 or more amino acids (*e.g.*, contiguous or consecutive amino acids) of the amino acid sequence of SEQ ID NO:2~~, or an amino acid sequence encoded by the DNA insert of the plasmid deposited with the ATCC as Accession Number _____~~.

At page 31, please replace the paragraph at lines 31-33 with the following text:

Preferred epitopes encompassed by the antigenic peptide are regions of COE-2 that are located on the surface of the protein, *e.g.*, hydrophilic regions, as well as regions with high antigenicity (see, for example, Figure 1~~Figure 2~~).

At page 40, please replace lines 9-31 with the following text:

A transgenic animal of the invention can be created by introducing a COE-2-encoding nucleic acid into the male pronuclei of a fertilized oocyte, *e.g.*, by microinjection or retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. The COE-2 cDNA sequence of SEQ ID NO:1 can be introduced as a transgene into the genome of a non-human animal. Alternatively, a non-human homologue of a human COE-2 gene, such as a rat or mouse COE-2 gene, can be used as a transgene. Alternatively, a COE-2 gene homologue, such as another COE-2 family member, can be isolated based on hybridization to the COE-2 cDNA sequences of SEQ ID NO:1 or 3~~, or the DNA insert of the plasmid deposited with ATCC as Accession Number _____~~ (described further in subsection I above) and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to a COE-2 transgene to direct expression of a COE-2 protein to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, both by Leder *et al.*, U.S. Patent No. 4,873,191 by Wagner *et al.* and in Hogan, B., *Manipulating the Mouse Embryo*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of a COE-2 transgene in its genome and/or expression of COE-2 mRNA in tissues or cells of the animals. A transgenic founder animal can

then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene encoding a COE-2 protein can further be bred to other transgenic animals carrying other transgenes.

At page 59, please replace lines 1-18 with the following text:

1. Diagnostic Assays

An exemplary method for detecting the presence or absence of COE-2 protein, polypeptide or nucleic acid in a biological sample involves obtaining a biological sample from a test subject and contacting the biological sample with a compound or an agent capable of detecting COE-2 protein, polypeptide or nucleic acid (*e.g.*, mRNA, genomic DNA) that encodes COE-2 protein such that the presence of COE-2 protein or nucleic acid is detected in the biological sample. In another aspect, the present invention provides a method for detecting the presence of COE-2 activity in a biological sample by contacting the biological sample with an agent capable of detecting an indicator of COE-2 activity such that the presence of COE-2 activity is detected in the biological sample. A preferred agent for detecting COE-2 mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to COE-2 mRNA or genomic DNA. The nucleic acid probe can be, for example, a full-length COE-2 nucleic acid, such as the nucleic acid of SEQ ID NO:1 or 3, ~~or the DNA insert of the plasmid deposited with ATCC as Accession Number _____,~~ or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to COE-2 mRNA or genomic DNA. Other suitable probes for use in the diagnostic assays of the invention are described herein.

At page 76, please replace the paragraph at lines 31-37 with the following text:

The nucleotide sequence encoding the human COE-2 is ~~shown in Figure 1 and is~~ set forth as SEQ ID NO:1. The protein encoded by this nucleic acid comprises about 584 amino acids and has the amino acid sequence ~~shown in Figure 1 and~~ set forth as SEQ ID NO:2. The coding region (open reading frame) of SEQ ID NO:1 is set forth as SEQ ID NO:3. ~~Clone Fbh18903, comprising the coding region of human COE-2, was deposited with the American Type Culture Collection (ATCC®), 10801 University Boulevard, Manassas, VA 20110-2209, on _____, and assigned Accession No. _____.~~

At page 77, please replace the paragraph at lines 30-32 with the following text:

Searches of the amino acid sequence of human COE-2 were performed against the HMM database (Figure 1~~Figure 2~~). These searches resulted in the identification of a "carboxylesterase domain" at about residues 25-569 of SEQ ID NO:2 (score = 558.6).